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Novel insights in the pathogenesis of Hodgkin lymphoma

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Chapter 1

Introduction and scope of this thesis

Introduction contents

1.1 General Introduction

Hodgkin lymphoma (HL) is a B cell malignancy that was described for the first time in 1832 [1]. It has an incidence rate of 3 per 100,000 person years in Western countries and is most common in adolescents and young adults [2]. HL has been divided into two disease entities, namely classical HL (cHL), which accounts for 95% of all cases and the less common nodular lymphocyte predominant HL (NLPHL). Nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted are the four cHL subgroups that are defined by the morphology of the tumor cells and the composition of the background [3]. Advances in radiation therapy and chemotherapy regimens have significantly increased the cure rate of patients with cHL. Currently, more than 80% of newly diagnosed patients younger than 60 years are cured. The 5-year disease-specific survival is 90% for patients with stages I and II, 84% for stage III and 65% for stage IV [4].

cHL is characterized by a minority of B cell derived tumor cells, named Hodgkin Reed-Sternberg (HRS) cells, which generally comprise less than 1% of the total cell population. The tumor mass contains a large majority of non-malignant reactive immune cells consisting of lymphocytes, histiocytes, eosinophils, and plasma cells. The HRS cells are large, sometimes bi- or multinucleated cells with prominent nucleoli [5]. HRS cells are derived from germinal center B cells, but they have lost the B cell phenotype as they show no expression of the B-cell receptor (BcR), and no or strongly reduced expression of many common B-cell markers and B-cell transcription factors [6, 7]. HRS cells have a characteristic CD20 negative to weakly positive, CD30+ and CD15+/− immunophenotype [8]. The presence of HRS cells in an abundant inflammatory infiltrate indicates that anti-tumor immune responses are insufficient for the eradication of HRS cells [8-10].

Epstein Barr virus (EBV) is present in the tumor cells in approximately 30% of the cHL patients in Western Europe and based on its monoclonal infection it has been proposed to play a causal role [11]. EBV positive HRS cells show a latency type II infection pattern that is restricted to expression of latent membrane protein (LMP)1, LMP2 and EBV-related nuclear antigen 1 (EBNA1). LMP1 and LMP2 mimic CD40 activation and BcR signaling respectively and thereby contribute to the malignant transformation of crippled B cells [12, 13]. EBV infection of HRS cells is associated with treatment failure in older adult cHL patients [14, 15].

1.2 Gene mutations in classical Hodgkin lymphoma

HRS cells usually show multiple chromosomal aberrations with both clonal and subclonal aberrations. Chromosomal translocations affecting the Ig loci, a hallmark of many B cell non-Hodgkin lymphomas (NHLs), occurs in about 20% of the cHL cases [16]. The BCL1, BCL2, BCL3, BCL6, REL and MYC genes were involved in some of these translocations with an Ig locus in HRS cells [16, 17]. Constitutive activation of the NF-κB pathway is one of the most consistent characteristics of HRS cells and can be caused by aberrations in genes involved in this pathway [18]. Amplifications of REL, encoding an NF-κB factor, were detected in about 30% of cHL cases [19, 20]. Mutations of NFKBIA and NFKBIE, the genes coding for the NF-κB inhibitors IκBα and IκBε, were found in 10%-20% of cases [21-24]. TNFAIP3, encoding the NF-κB inhibitor A20, is mutated in HRS cells in 40% of cHL cases [25, 26]. Most of the TNFAIP3 gene mutations are observed in EBV negative cHL cases, indicating that inactivation of A20 and infection with EBV may represent two alternative mechanisms for the malignant transformation of HRS cell precursors [26]. TNFAIP3 overexpression in A20 deficient cHL cell lines impairs growth and survival, indicating that TNFAIP3 acts as a tumor suppressor gene in cHL [26]. The alternative NF-κB pathway is activated by genomic gains of MAP3K14 (NIK), which is a positive regulator of this pathway, in 25% of the cHL cases [27, 28]. Aberrations of other known regulators of the classical NF-κB pathway, i.e. mutations of CYLD in the classical NF-κB pathway, of TRAF in the alternative NF-κB pathway and genomic gains or translocations of BCL3 are rarely detected in HRS cells [27, 29].

Genetic aberrations are also found in the JAK/STAT signaling pathway which is frequently activated in HRS cells [30]. JAK2, a STAT activator, shows chromosomal gains in about 25% of the cHL cases and translocations in rare cases [31, 32]. SOCS1, a main STAT inhibitor, shows inactivating mutations in 40% of cHL cases [33]. The JAK2 genomic region on 9q24 shows copy number gains in HRS cells. This genomic region also contains the KDM4C (JMJD2C) and the programmed death ligand 1 and 2 (PD-L1, PD-L2) gene loci [34, 35]. KDM4C encodes a histone demethylase that specifically demethylates 'Lys-9' and 'Lys-36' residues of histone H3. Downregulation of KDM4C induced cell death in HL cell lines [34]. PD-L1 and PD-L2 inhibit the functionality of PD-1 positive T cells and thereby contribute to the immunosuppressive microenvironment in HL [35].

Approximately 15% of the cHL cases have a translocation involving the MHC class II transactivator (CIITA) gene locus, which is the master regulator of HLA class II expression [36]. This translocation disrupts the CIITA gene and thereby induces HLA class II downregulation [37]. The PD-L1 gene is the translocation partner of the CIITA chromosomal translocations resulting in enhanced expression of PD-L1 and PD-L2 [37]. Other genes that were mutated in HRS cells include FOXO1, PTPN2, TP53, FAS, CD95, ATR and ATM, but in general these genes were mutated only in rare cases [38-44].

Genes related to HL susceptibility and genes mutated in familial cases of cHL

Genome-wide association studies of HL identified several susceptibility loci, i.e. at 5q31 (IL13), 6p21 (HLA class I and II), 2p16.1 (REL), 8q24.21 (PVT1) and 10p14 (GATA3) [45, 46]. HL is one of the lymphomas with the strong familial association [47]. KLHDC8B was found as a constitutional translocation partner fusing its 5'-UTR to an intergenic region on chromosome 2q11.2 in the germline of a family with several HL patients [48]. A rare SNP at a highly phylogenetically conserved position within the 5'-UTR reducing KLHDC8B protein expression was linked to cHL in three other families [48]. The function of KLHDC8B is not completely clear, but downregulation of this gene leads to accumulation of binucleated cells which is a feature of HL. A germline replacement mutation in NPAT was observed at a significantly increased frequency in cHL patients as compared to healthy controls [49]. The functional relevance of this NPAT mutation in HRS cells is still unknown. Lawrie et al. (2012) found non-synonymous SNPs in FAM107A, ALS2CL and IGSF3 in all four analyzed cHL patients of one family and proposed a putative role of these genes in cHL development. Two of these three genes (FAM107A and ALS2CL) are located on chromosome arm 3p, have been implicated as candidate tumor suppressor genes in other malignancies. Overall, the gene loci linked to familial HL were not identified as gene susceptibility loci in the GWAS nor found to be somatically mutated in cHL cell lines or HRS cells.

1.3 Human Leukocyte Antigen (HLA) expression in cancers

The classical HLA class I heavy chains are products from the polymorphic HLA-A, HLA-B and HLA-C genes and present endogenous antigens to CD8+ T cells. These heavy chains are stabilized by β2-microglobulin (β2-m) and are expressed on the

cell surface in the context of HLA class I [50]. Transporters of antigenic peptides (TAP1, TAP2) and tapasin are involved in antigen processing required for correct cell surface presentation. HLA-G a non-classical HLA class I gene, is the ligand for inhibitory receptors that are present on NK cells and subsets of T lymphocytes [51]. Another non-classical HLA class I gene, HLA-E, interacts with the inhibitory receptor CD94/NKG2A on NK cells and a subset of the CD8+ T lymphocytes [52-54]. Expression of both HLA-G and HLA-E can protect HLA class I negative cells from NK and CTL cell mediated cytotoxicity via binding to inhibitory receptors expressed by NK and CTL cells [55, 56].

Classical HLA class II molecules consist of two heavy chains referred as the A and B chains that associate to form functional HLA-DR, HLA-DP and HLA-DQ antigen presenting complexes. These complexes are expressed on the cell surface of professional antigen presentation cells (APCs) and can present antigenic peptides to CD4+ T cells. HLA-DM is a non-classical HLA class II molecule that is required for the removal of the invariant chain derived CLIP peptide from the peptide binding groove of the classical HLA class II genes. This removal is essential for the proper loading of antigenic peptides in the HLA class II antigen binding groove [57]. HLA-DM can enhance further peptide exchanges and favor peptides with the highest affinity for class II molecules. In this way, HLA-DM can narrow the repertoire of presented peptides [58]. HLA-DO, the other non-classical HLA class II molecule partially inhibits HLA-DM function [58] and thereby broadens or alters the population of peptides presented to CD4+ T cells [59]. We previously found that absence of HLA-DM leads to retention of the non-immunogenic CLIP in the antigen binding groove of HLA class II in cHL cases (unpublished data). This mechanism has also been shown in cHL cell lines [60]. HRS cells often retain their professional antigen presentation capability including expression of molecules involved in antigen presentation such as HLA, TAP1, TAP2, invariant chain, co-stimulatory (B7, CD40, CD70) and cell adhesion molecules (ICAM-1 and LFA-3) that aid in activation of antigen specific T cells [61].

1.3.1 HLA expression in Hodgkin Reed-Sternberg cells

In EBV- cHL, retention of HLA class I expression has been observed in 14% of cHL cases and retention of HLA class II expression in 50% of the cases. In contrast, retention of HLA class I and class II can be found in up to 70% of EBV+ cHL cases [62-64]. Complete loss of HLA class II expression is an adverse prognostic factor [64]. A proportion of the EBV+ cHL cases shows enhanced HLA class I and/or II expression as compared to the surrounding lymphocytes [65]. This is quite remarkable, since HLA class I restricted immune responses to EBV should kill the EBV+ HRS cells [65, 66] and HLA class II restricted CD4+ cells control the EBV infection and malignant transformation in vitro [67]. Thus, it is enigmatic why HLA retention is prominent in EBV+ cHL patients and less pronounced in EBV- cHL. The mechanism of HLA loss in cHL is unknown.

1.3.2 HLA expression in NHL

NHLs constitute a wide variety of lymphoma entities that in contrast to HL consist of a majority of tumor cells. Loss of HLA protein expression has also been observed in several NHL subtypes, which is less frequent as compared to cHL [68, 69]. Loss of HLA is partly due to loss of the 6p21 chromosomal region in follicular lymphoma and extra-nodal diffuse large B cell lymphoma [70]. It has been shown that loss of heterozygosity for one allele coincides with mutations in the remaining allele causing complete loss of HLA class I and II genes in some diffuse large B cell lymphomas [71, 72]. Sixteen DLBCL samples (13/111 biopsies and 3/23 cell lines) both B2M alleles were inactivated due to homozygous deletions (8 cases), biallelic mutations (4 cases) and hemizygous deletions with inactivating mutation of the second allele (4 cases)[73]. In the remaining cases, the mechanisms of complete HLA loss remain unknown.

1.4 Chromatin remodeling proteins: PML and SATB1

The DNA strands within an interphase nucleus are held on a scaffold structure with multiple loops that can vary in size. As a basic unit, these chromatin loops are essential for DNA replication, transcription regulation and chromosomal package. Chromatin loops are anchored to the nuclear matrix by short DNA sequences of about 100-2000bp called matrix attachment regions (MARs) [74, 75]. The best-characterized components of the nuclear matrix include lamins, topoisomerase II, special AT-rich sequence binding protein 1 (SATB1) and scaffold attachment

factor-B1 (SAFB1). These genes are key players in fundamental nuclear processes such as DNA transcription and replication [76-79]. SATB1 was recognized as the first cell-type-restricted MAR-binding protein. Ottaviani et al detected a high density of MARs in the HLA gene locus in B-lymphoblastoid cells. Within the HLA genomic region, over 91% of all MARs identified are present in the HLA class I (44%) and class II (47%) regions, while the remaining 9% are within the class III and extended class II regions [80]. Promyelocytic leukemia protein (PML) and SATB1 forms a complex with promyelocytic leukemia protein and organizes chromatin loops by binding to MAR sites in the HLA locus of Jurkat cells [81].

1.4.1 Promyelocytic leukemia protein

Promyelocytic leukemia protein (PML) is the main component of nuclear bodies (NBs). PML-NBs are discrete nuclear foci of 0.2 to 1.0μm that are present in the nuclei of most mammalian cells. PML-NBs appear to be associated with the nuclear matrix, as evidenced by fractionation experiments and DNase and RNase resistance [82]. PML-NBs are dynamic nuclear matrix-associated domains that recruit a variety of proteins and regulate many nuclear functions such as DNA replication, transcription and epigenetic modifications [83]. There are 5 to 30 PML-NBs per nucleus depending on the cell type, cell cycle phase and differentiation stage [84]. PML-NBs organize the HLA locus into distinct chromatin loops [81, 85, 86]. The PML transcript can be processed into seven different splice variants resulting in protein isoforms that have variable C-termini [87]. These isoforms may have partly different functions in expression regulation in general and more specifically also of the HLA genes (summarized in Table 1). Exogenous PML-VI induces the expression of HLA class I heavy chain and β2-m in lung cancer cell lines [88]. Silencing of PML-III or V results in a reduced HLA-A but an enhanced HLA-G expression in Jurkat cells [81]. Knockdown of all PML isoforms by shRNA inhibited the IFN-γ-induced HLA class II and CIITA expression in a cervical carcinoma cell line and lung fibroblasts. PML-II forms a complex with CIITA which stabilizes CIITA at PML-NBs. PML-NBs may act as co-regulators of IFN-γ-induced HLA class II expression via a functional interaction of PML-II and CIITA [89]. Furthermore, PML isoform IV interacts with H3K4-methyltransferase complex (MLL) in HeLa cells upon IFN-γ treatment and co-activates the transcription of HLA-DRA [90].

Table 1. The effect of HLA expression after overexpression or knockdown of PML and SATB1 in vitro.

Cell lines	PML isoforms and SATB1	HLA genes	References
Lung cancer	PML-VI↑	HLA-ABC↑	[88]
T lymphoma (Jurkat)	PML-III↓	HLA-A↓ HLA-G↑	[81]
	PML-IV↓	HLA-G↓	
	PML-V↓	HLA-A↓ HLA-G↑	
	SATB1↓	HLA-A↑ HLA-G↑	
cervical cancer (HeLa)	Pan-PML ↓	IFN-γ-induced DRA↓	[90]
Lung fibroblasts	Pan-PML↓	IFN-γ-induced HLA class II transactivator (CIITA)↓ HLA-DMB and	[91]

1.4.2 Special AT-rich sequence binding protein 1

SATB1 (special AT-rich sequence binding 1) is a protein that is expressed predominantly in thymocytes and T cells and also in absorptive cells of intestinal epithelium, osteoblasts, ameloblasts, and fetal neurons [92]. It regulates gene expression by folding chromatin into loop domains, tethering MAR sites to an SATB1 network structure [78, 93, 94]. Ablation of SATB1 by gene targeting results in temporal and spatial misexpression of numerous genes and arrested T-cell development, suggesting that SATB1 is a cell-type specific global gene regulator [93]. SATB1 deficient mice die soon after birth as they do not develop T cells. SATB1 partially resides within PML-NBs and has been shown to organize the HLA class I locus into distinct loops. Silencing of SATB1 in Jurkat cells results in an

enhanced expression of HLA-A, HLA-G, HLA-H and HCG4P6 [81]. To date, there are no studies that link SATB1 to the regulation of HLA class II expression.

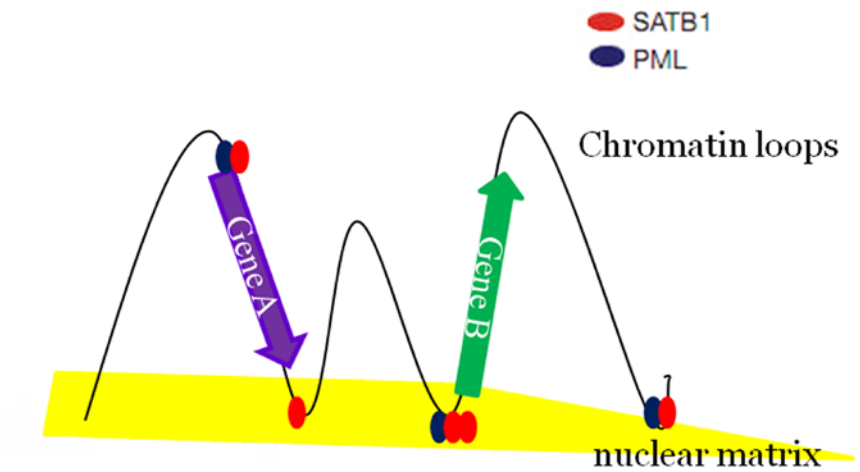

Figure 1. Schematic representation of occupancy of SATB1 and PML at MAR sites in relation to chromatin loop structures (black line). Gene A and B have been indicated by an arrow specifying their transcriptional direction. The yellow colored platform at the base of the chromatin loops indicates the nuclear matrix. The interaction between SATB1 (red dots) and PML (blue dots) occurs in PML nuclear bodies and they organize the chromatin loops by directly binding to DNA sequences at the matrix and up or downstream regulatory sequences in the loops.

Scope of this thesis

In this thesis we aimed to study the pathogenesis of HL to gain more insight in the role of the microenvironment, genes involved in the malignant transformation and the mechanisms leading to HLA loss in cHL and other cancer subtypes. **Chapter 2** is a review of cHL focusing on how HRS cells evade effective anti-tumor response and shape the microenvironment to their own benefit. In **Chapter 3**, we sequenced the exomes of cHL cell lines and identified recurrently mutated genes. Next, we determined if these mutated genes were located in chromosomal regions with copy number variations or differentially expressed in cHL cell lines compared to germinal center B cells. In the second part of this thesis, we focused on HLA expression in cHL and two types of solid tumors. The mechanisms of enhanced or complete loss of HLA expression in malignant cells are not well-studied. In this thesis, we determined the role of two chromatin remodeling proteins, PML and SATB1 in the regulation of HLA expression. In **Chapter 4**, we investigated the association between PML-NBs, SATB1 and HLA class I expression in EBV+ cHL. Furthermore, we analyzed if HLA class II expression in HRS cells is associated with the number of PML-NBs and SATB1 expression in **Chapter 5**. In addition, we determined the correlation between specific PML isoforms and multiple HLA class II genes at the mRNA level in cHL cell lines. Downregulation of HLA class I has also been frequently observed in many types of epithelial cancers, such as human papillomavirus (HPV) associated oropharyngeal squamous cell carcinoma (OpSCC) and ovarian cancer. In **Chapter 6A**, we studied OpSCC and determined if the number of PML-NBs and SATB1 are associated with HLA class I expression in HPV positive and negative tumor cells. In **Chapter 6B**, we studied the association between PML-NBs and HLA class I expression in ovarian cancer.

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